Supreme Court, U.S.
FILED
031237 MAR 02 2004
OFFICE OF THE CLERK
No.

IN THE
Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE and TELIOS PHARMACEUTICALS, INC.,

Respondents.

On Petition for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR WRIT OF CERTIORARI

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March 2, 2004

QUESTION PRESENTED

To encourage development and expedite introduction of pharmaceuticals, Congress amended the patent laws in 1984 to insulate drug research from charges of infringement so long as the research is "reasonably related to the development and submission of information" to the Food and Drug Administration. Did the Federal Circuit err in concluding that this drug-research safe harbor does not protect animal studies of the sort that are essential to the development of new drugs, where the research will be presented to the FDA, and where barring the research until expiration of the patent could mean years of delay in the availability of life-saving new drugs?

LIST OF PARTIES AND RULE 29.6 STATEMENT

The names of the parties before the United States Court of Appeals for the Federal Circuit appear in the caption of the Petition for Writ of Certiorari. The Scripps Research Institute and Dr. David A. Cheresh were identified as "defendants" in the caption adopted by the Court of Appeals but had been dismissed from the case before the appeal was filed and did not appear before the Court of Appeals.

Petitioner, Merck KGaA, has no parent corporation, and no publicly held companies own 10% or more of Merck KGaA stock.

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OPINIONS BELOW

The opinion of the U.S. Court of Appeals for the Federal Circuit is reported at 331 F.3d 860, but the reported opinion does not include an "errata sheet" issued by the court on December 3, 2003. App. 36a-37a. The District Court order reviewed by the Court of Appeals is not reported. App. 47a-50a.

JURISDICTION

The judgment of the Court of Appeals was entered on June 6, 2003, and rehearing and rehearing en banc were denied on December 3, 2003. The jurisdiction of the Court of Appeals was based on 28 U.S.C. § 1295(a)(1). This Court's jurisdiction is invoked under 28 U.S.C. § 1254(1).

STATUTORY PROVISION

35 U.S.C. § 271(e)(1):

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other process involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

INTRODUCTION

Cancer. Rheumatoid arthritis. AIDS. Heart disease. Alzheimer's. Multiple sclerosis. The list could go on for volumes. Deadly diseases, painful disorders, heart-wrenching conditions that afflict millions of people. All of them no doubt find themselves hoping against hope that someone, somewhere will discover a drug that could cure them or relieve their suffering—and get it to them soon. This case is about how quickly many of those prayers will be answered. The stakes are measurable in millions of lives.

The Federal Circuit has interpreted the patent laws to allow the holder of a patent on a chemical compound to enjoin a medical researcher from conducting animal studies that simulate human disease and that could yield ground-breaking cures for people. The patent holder may bar all laboratory tests using the compound itself or on structurally similar compounds, even if (as is the case here) it has not found any commercial use for the compound, and even though any new drug developed by the medical researcher would not and could not be marketed until after all relevant patents expire. Drug innovators and researchers will have to sit on their hands awaiting patent expiration before *starting* to conduct the battery of experiments necessary to qualify a potentially path-breaking new drug for clinical trials involving human subjects, which, in turn, take many years to complete. Consequently, potential cures or remedies for innumerable diseases and conditions will be denied to patients until long after all patents expire.

The Federal Circuit could reach this conclusion only by devising a non-textual and unprecedented reading of a drug-research safe harbor provision that Congress devised to avoid just such an unwelcome result. The provision in

question provides that "it shall not be an act of infringement to . . . use . . . a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs." 35 U.S.C. § 271(e)(1). The immediate impetus for this safe-harbor provision was the need to undo the mischief of another Federal Circuit opinion, which had held that a researcher infringes a patent by conducting experiments on a generic version of a drug already on the market with a view toward generating the data necessary to secure FDA approval to market the generic once the patent expires. *See Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858 (Fed. Cir. 1984). Congress concluded that the holder of a patent should not be permitted to secure a *de facto* extension of its patent term by enjoining a researcher from conducting the sorts of experiments necessary to position a drug to get to the market upon patent expiration. In other words, because the research necessary for FDA approval takes so long, and the imperative to move drugs to patients is so strong, Congress has authorized drug developers to get a head start on the research without fear of patent-infringement suits.

A panel of the Federal Circuit—in a split decision with a spirited dissent—once again has adopted the most restrictive possible interpretation. In the majority's view, clinical studies with humans are "reasonably related" to the drug approval process, but the animal studies that are a necessary prerequisite to any clinical study—and that invariably are also submitted to the FDA—are not.

Under the panel's interpretation, the safe harbor protects manufacturers of generic drugs mimicking products already on the market, for they can piggyback on the extensive animal and human studies already performed by a drug

innovator with whom they intend to compete. But the protection does not extend to an innovator prepared to spend millions to test a pioneer drug that could be a more effective cure, or that could be safer, than any drug on the market, because no such drug can ever go straight to clinical studies on humans without first being subjected to extensive animal tests.

Thus, the practical consequence of the Federal Circuit's distinction is that the safe harbor protects only copy-cats, not innovators.

The Federal Circuit's holding has rocked the scientific and healthcare communities. Overnight, the Federal Circuit has transformed the United States from the world's premier new-drug innovator and the site of some 80 percent of worldwide research on new drugs into hostile territory for drug innovation. Because all patent cases are appealable only to the Federal Circuit, this opinion will be the last word on the subject—unless this Court intervenes to review this case. The ramifications of a ruling, in either direction, are so far-reaching that this case warrants this Court's review.

STATEMENT

Beginning in 1988, Merck KGaA, a German pharmaceutical company, began to support the research of a top scientist at the prestigious Scripps Research Institute in California who was studying one of the mechanisms for cancer growth. App. 26a. By 1995, the research at Scripps in coordination with Merck's own medicinal development had led to the discovery that a particular drug—in a family of organic chemicals called cyclic peptides—was especially promising as an anti-cancer drug and also as a treatment for rheumatoid arthritis and blindness from macular

degeneration. App. 26a-27a. The peptide operates by essentially shutting down the growth of blood vessels, thus starving tumor cells and reducing unwanted vascular growth in the joints and retina. App. 27a.

As memorialized in a collaboration agreement signed with Merck in 1995, the Scripps team devised an integrated, focused series of animal studies using that drug provided by Merck, and then a year later using an even more promising derivative of the same peptide. App. 28a. The terms of the funding obligated the researchers to conduct the "necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials." App. 5a. In other words, Merck paid teams of scientists at Scripps to conduct a battery of animal tests and develop all the data the FDA might require before it would permit the drug to advance to clinical trials on human subjects. *Id.* Furthermore, if the drug proved to be safe and effective, Merck hoped to obtain FDA approval to market its drug for administration to cancer patients no sooner than ten years after the animal testing began. A7377.[1]

Moreover, based in part on the Scripps research demonstrating the promise of this potential new drug in chicken eggs, mice and rabbits, the National Cancer Institute (NCI) agreed to sponsor clinical trials in humans. A6655-59. Those trials are proceeding now.

Respondents Telios Pharmaceuticals, Inc. and Integra LifeSciences I, Ltd. (collectively, Integra) sued Merck, Scripps and the lead scientist to stop the experiments cold. The 1996 lawsuit claimed that the Scripps research infringed

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[1] Citations to "A___" are references to the Joint Appendix filed below.

several patents filed by Telios's founders. Telios had never discovered a commercially viable use for those patents, though it went bankrupt trying. A5615-16. Nor had Integra developed any application for the patents it inherited when it bought Telios in the bankruptcy sale. The patents are due to expire between 2003 and 2006, before Merck can realistically market its potentially life-saving cancer drug. Nevertheless, Integra sought an injunction. App. 42a.

A jury found that at least a few of the Scripps experiments infringed the patents and awarded $15 million in damages. On appeal to the Federal Circuit, Merck argued, as it had to the district court, that the experiments fell within the drug-research safe harbor Congress carved out of the patent laws, which provides:

> It shall not be an act of infringement to . . . use . . . a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs.

35 U.S.C. § 271(e)(1).

Even though the district court found that "much of the evidence at trial established that the accused experiments generated the types of information that are submitted to the FDA," App. 40a, and even though Merck intended to submit all the data from the Scripps experiments to the FDA in its application for permission to conduct clinical trials and did in fact submit such data to the NCI to recruit it as a partner in the clinical trials, A6650-55, a split panel of the Federal Circuit held that the drug-research safe harbor did not cover those experiments. The panel reached that conclusion by misinterpreting "reasonably related to . . . submission of

information" to the FDA as a requirement that the experiments be directly related "to information the FDA considers *in approving* a drug," as contrasted with experiments producing information the FDA considers in approving human trials for a new drug—such as the information gathered at Scripps. App. 13a (emphasis added).

The panel's limiting interpretation was rooted in a constricted view of the legislative history. The panel noted that the immediate impetus for the passage of the safe harbor provision was another Federal Circuit opinion that Congress found untenable. *See Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858 (Fed. Cir. 1984). In that case, the Federal Circuit held that a researcher infringes a patent by conducting experiments on a generic version of a drug already on the market with a view toward generating the data necessary to secure FDA approval to market the generic once the patent expires. From this impetus, the panel drew the conclusion that "the express objective of the 1984 Act was to facilitate immediate entry of safe, effective *generic* drugs into the marketplace upon expiration of a pioneer drug patent." App. 12a (emphasis added). And, only by reading this impetus as a limit, could the Federal Circuit reject "an interpretation of [the safe-harbor provision] that would encompass drug development activities far beyond those necessary to acquire information for FDA approval of a patented pioneer drug *already on the market*," i.e., beyond the development of a generic drug. App. 13a (emphasis added).

Judge Newman dissented, objecting especially to the proposition that the "'safe harbor' does not apply to federal registration of pioneering new drugs like the Scripps/Merck products here at issue, but only to registration of generic copies of drugs for which the patent is about to expire."

App. 32a. She observed both that "the statute has been interpreted as of broader scope," *id.* (citing *Eli Lilly & Co. v. Medtronic Inc.*, 496 U.S. 661 (1990)), and that the parties themselves all assumed that the safe harbor covers new drugs, not just generics. App. 32a-33a.

REASONS FOR GRANTING THE WRIT

This Case Is of Profound National Importance Because the Scope of the Drug-Research Exemption to the Patent Laws Could Mean Life or Death for Millions of Patients.

Generics vs. pioneer drugs

In the world of drug development there are generics and there are new drugs. The difference is critical to both an understanding of the Federal Circuit's opinion and an appreciation of the profound ramifications of this case to research scientists, drug innovators, the nation's stature as the leading incubator for new drugs, and, most important of all, patients who are sick or dying.

Generics are mimics of drugs already on the market. By definition, they have no new curative properties; they are neither safer nor more effective than the drugs patients are already taking—they are just copies. Their promoters cannot claim that they will save more lives or enhance the quality of life for any patient. Their main societal value is to enhance price competition.

The real life-savers are new drugs. A new drug, or "pioneer drug," differs from any drug that is already being administered to patients. It might cure a disease that no other drug cures. It might be more effective at curing a disease or relieving symptoms than other drugs on the

market. Or it might have fewer or less severe side effects. The availability of new drugs could enhance price competition, too, but their primary value lies in their novelty, in their unique life-saving, disease-curing, or palliative effects.

This difference between generics and new drugs translates into a stark difference in regulatory approval. The process for testing and FDA approval of a new drug is extensive, expensive, and lengthy. Step One is the generation of data for the FDA to determine whether to allow the testing of the drug as an Investigational New Drug (IND) in human clinical trials. 21 U.S.C. § 355(i). The purpose of such an application is to satisfy the FDA that the new drug is safe enough and potentially valuable enough to justify clinical testing in humans. *See id.* § 355(i)(3) (application must be denied if "the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation"); 21 C.F.R. § 312.23(a)(3)(iv) (requiring submission of "[t]he *rationale* for the drug or the research study") (emphasis added). As part of an IND, the innovator is statutorily required to submit the results of so-called "preclinical tests (including tests on animals)." 21 U.S.C. § 355(i)(1)(A); *see* 21 C.F.R. § 312.1 (describing "procedures and *requirements* for the submission to, and review by, the Food and Drug Administration of investigational new drug applications (IND's)") (emphasis added); *see also* 21 C.F.R. § 312.23(a)(5)(i)-(iii), (a)(7)-(8). Specifically, the FDA requires both test tube and animal studies pertaining to toxicology, mechanism of action (how the drug works), pharmacology (the drug's effects), and pharmacokinetics (how quickly the drug is absorbed and eliminated by the body). *Id.* § 312.23(a)(5)(ii)-(iv). It requires the innovator to justify the human experimentation by demonstrating the

potential therapeutic value of the drug and including its effectiveness in animal models. *Id.* § 312.23(a)(8)(i) (requiring full data on "the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known"); *see also* A7404-09, A10594-95.

Only if the FDA is satisfied with the extensive pre-clinical data accumulated in Step One can an innovator turn to Step Two, another multiple-year battery of experiments, this time on human subjects. *See* 21 U.S.C. § 355(c)-(e), (i). Based on both these clinical data and the data required for Step One, the innovator submits a New Drug Application (NDA) to the FDA. The FDA will not approve the drug for public use unless the data prove that it is both safe and effective. 21 U.S.C. § 355(d).

For generics, the approval process is simpler and speedier, precisely because a generic drug does nothing new. The aspiring manufacturer of a generic piggybacks on the years and millions of dollars the drug innovator invested in the product to bring it to market in the first place. It does not have to prove, in animal or clinical studies, that the drug is safe and effective, but only that the particular version proposed has the same composition as, and is "bioequivalent" to, the pioneer drug it is mimicking, *id.* § 355(j)(2)(A)(iv), which is to say that the body absorbs them the same way, *id.* § 355(j)(8)(B). The manufacturer presents these data to the FDA in a one-step application called an Abbreviated New Drug Application (ANDA). *See id.* § 355(j).

The pervasive understanding of the safe harbor

Whether a drug is a path-breaking new drug or a mimicking generic, it could be subject to a patent held by another. If so, it cannot be marketed before the patent expires (unless, of course, the patent holder chooses to grant a license or the patent is defeated). So the question in this case is not whether new drugs will be sold during the patent term, but rather how soon *after patent expiration* these drugs can be marketed. Does the drug-research safe harbor authorize a drug innovator to get a head start on the long process necessary for securing FDA approval, so that the drug can be released shortly after patent expiration? Or does the patent holder have the right to sue to enjoin any such testing for the entire patent term?

For nearly 20 years, since the 1984 passage of the drug-research safe harbor, it has been understood that the safe harbor authorizes both mimickers and innovators to get a head start on FDA approval. Those engaged in drug development, like the defendants here, believed that they could conduct all the routine experiments along the way to secure FDA approval so that the drug can get into patients' hands soon after the patent expires.

That is what the cases consistently held. As the leading case, affirmed by the Federal Circuit, observed in the analogous context of pre-clinical testing of medical devices, "because safety certification . . . was necessary in order to obtain import approval *and conduct clinical tests*, the . . . tests necessary to obtain that certification would have to be considered reasonably related to the generation of data for submission to the FDA." *Intermedics, Inc. v. Ventritex, Co.*, 775 F. Supp. 1269, 1285 (N.D. Cal. 1991) (emphasis in original), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993); *see Amgen,*

Inc. v. Hoechst Marion Roussel, Inc., 3 F. Supp. 2d 104 (D. Mass. 1998); *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, No. 95 Civ. 8833, 2001 WL 1512597 at *6 (S.D.N.Y. Nov. 28, 2001); *Nexell Therapeutics, Inc. v. Amcell Corp.*, 199 F. Supp. 2d 197, 204 (D. Del. 2002); *cf. Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520, 1523 (Fed. Cir. 1992) (trade show displays of medical devices to solicit clinical investigators for clinical trials were exempt activities because "device sponsors are responsible for selecting qualified investigators and providing them with the necessary information to conduct clinical testing").

The courts recognized that this was the plain meaning of the safe harbor provision. Congress did not limit the drug-research safe harbor to "the development and submission of information necessary for approval of a generic drug" or (as the Federal Circuit put it) "drug development activities [not] far beyond those necessary to acquire information for FDA approval of a patented pioneer drug already on the market." App. 13a. Nor did Congress limit the sanctuary to "the development and submission of clinical data in humans" or of "information to be included in a New Drug Application [Step Two], but not in an *Investigational* New Drug application [Step One]." Rather, the safe harbor covers broadly "the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs," which is to say "the development and submission of information"—any information—to the FDA, or any activities "reasonably related" to the generation of that sort of information.

The courts also understood that this result was dictated by the policy underlying the safe harbor. The point of the safe harbor provision, or so everyone believed, was to preclude a patent holder from securing a *de facto* extension

of its patent term by enjoining research necessary to FDA approval. That policy justification applied with even greater force to pioneer drugs than to generics, both because of their greater value to sick and dying patients and because of the prolonged process for FDA approval for a new drug. And since a new drug necessarily must go through Step One in order to get to Step Two, it would have made no sense for Congress to provide a safe harbor for the former but not for the latter. *See Bristol-Myers Squibb Co.*, 2001 WL 1512597 at *6 (the "contention that Section 271(e)(1) only applies after a drug candidate has been selected or filed with the FDA would have the effect of preventing competitors from experimenting with patented inventions in order to create new or improved drugs," a result that "would seem to negate Congress's intent to have new drugs come to market without delay upon the expiration of a patent").

Any doubt as to Congress's intention—and, specifically, as to whether the safe harbor, despite its language, was limited to generics—was laid to rest in 1990. That was when this Court held that the safe harbor provision covers not just generic drugs, and indeed not just drugs, but the "entire statutory scheme of regulation" under the FDA's domain, *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 666-67 (1990), including "medical devices, food additives, color additives, *new drugs*, antibiotic drugs, and human biological products," *id.* at.674. *See also AbTox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1025 (Fed. Cir. 1997) (extending *Eli Lilly*, with the premise that the safe harbor refers to "an entire statutory scheme of regulation," not merely to particular subsections related to generic drugs).

The judiciary's uniform interpretation has translated into a pervasive understanding in the regulated industry in the U.S. and abroad and in the scientific community across the

nation that the safe-harbor provision provides broad protection to "all activities associated with the development of new drugs and medical devices subject to FDA approval," William Feiler, *Expanding Exemptions for Generics*, Managing Intellectual Property 46 (June 1, 2003), and that "courts will maintain the expansive depth and breadth of the Hatch-Waxman Act's safe harbor in the foreseeable future." Phillip B.C. Jones, *Navigating the Hatch Waxman Act's Safe Harbor*, 57 Food Drug L.J. 475, 488-89 (2002). Scientists and drug innovators took it for granted that they could conduct any studies, whether in humans, animals, or petri dishes, relevant to evaluating the safety and therapeutic promise of potential new drugs, "as long as a cogent argument could be made that the conduct was 'reasonably related' to seeking FDA approval." Brian D. Coggio, *The Safe Harbor Provision of the Hatch-Waxman Act: Present Scope, New Possibilities, and International Considerations*, 57 Food Drug L.J. 161, 166 (2002).

The import of the Federal Circuit's shift

Thanks in no small measure to the safe harbor, patients have benefited from the prompt testing and release of new drugs. What's more, our country has earned the status as the world's innovator for new drugs. The United States is host to 80% ($26.4 billion out of $32 billion) of the worldwide research on new drugs. *See* Pharmaceutical Research and Manufacturers of America, *Industry Profile* (2003) at 10 *at* http://www.phrma.org/publications/publications/profile02/index.cfm. U.S.-based research institutions—like Scripps—have flourished. Foreign companies—like Merck—have opted to partner with U.S. research institutes to assess the safety and efficacy of their drugs, rather than conduct the research in any number of other potential sites outside the U.S. Both have been comforted by the pervasive

understanding, articulated by the lower courts and sanctioned by the Federal Circuit until now, that the safe harbor (and particularly the language "reasonably related to") gives wide berth to researchers to conduct all manner of drug studies, "because it will not always be clear to parties setting out to seek FDA approval for their new product exactly what kinds of information, and in what quantities, it will take to win that agency's approval." *Intermedics*, 775 F. Supp. at 1280; *see Nexell Therapeutics*, 199 F. Supp. 2d at 204-05.

All this has been jeopardized by this case, which represents the first time that a court has even suggested that the drug-testing safe harbor covers only the ultimate phase in the drug-approval process, but not other activities that generate information for submission to the FDA. Whether the Federal Circuit is right, or all the past precedent is right, there is no disputing that the answer to the question presented is of great moment.

It matters first and foremost to the millions of patients who need new drugs. Now, not a decade or more from now.

It matters to the scientific community, which, to quote one commentator, has just been hit with a "Bombshell." Dan Reisner, *Pre-Clinical Research Bombshell: Court Rules: No Exemption from Patent-Infringement Claims*, 23 Pharms. Executive 38 (Dec. 1, 2003). The researcher's relentless search for new insights into the mechanisms and cures of diseases depends, as the Scripps research in this case did, upon a healthy symbiosis with the pharmaceutical industry. That synergy is now, according to the Federal Circuit, at war with the patent laws. Under the threat of litigation, Scripps stopped not only the cancer research that was the subject of this lawsuit, but also research on close relatives of the drug that seemed to be promising as cures of

other diseases such as rheumatoid arthritis. In the wake of the Federal Circuit's opinion, other researchers like Scripps are being advised to "take greater stock of their pre-clinical investigations," *id.*, and to "consider re-examining their use of patented technology in pre-clinical Research and Development activities," Pillsbury Winthrop, *Integra's Win May Give Cause for Re-evaluation of Future Exploratory Activities*, Client Alert (Aug. 6, 2003) *at* http://www.pillsburywinthrop.com/topics/results.asp?what=integra. So researchers nationwide are grappling with the untenable choice between shutting down their ongoing research and taking the risk, with every mouse they inject, that expensive lawsuits and crushing potential liability are just around the corner.

It matters to Congress, which depends on the courts to properly interpret the statutes it passes. Congress was remedying a Federal Circuit opinion when it carved out the drug-research safe harbor, in the first place, and it should not be forced to revisit this matter, yet again, because the Federal Circuit has now disregarded the plain text of the safe harbor provision it introduced.

It matters, of course, also to the pharmaceutical industry—or at least to that sector of the industry that accepts the challenge of finding cures. For this sector, it is no answer to assume, as the Federal Circuit seems to have, that the same research will continue, so long as drug innovators are willing to pay licensing fees. The reason Congress had to pass the drug-research exemption in the first place was that some patent holders were all too happy to exercise their absolute right to withhold a license and preserve their market position, or just to play the dog in the manger blocking valuable uses of a drug even though (like Integra) they found no commercially viable use themselves.

When a lower court departs as drastically from existing precedent as the Federal Circuit has in this case, and has created as much uncertainty, the natural instinct for a court of last resort is to let the issue percolate, to see whether the lower court, itself, clarifies, and whether a chorus of other circuits rises up in disagreement. That is not a viable option here. First, this issue will not percolate among the circuits, and there can be no circuit conflict, because the Federal Circuit, as the exclusive forum for all patent appeals, has the last word on the matter—subject only to this Court's intervention. Second, the consequences of this case are so profound that the luxury of time is not available. Diseases do not wait.

CONCLUSION

This case affects the availability of new drugs for millions of sick and dying patients and the future of biomedical research in this country. The Federal Circuit has narrowed a protection for drug research that drug innovators and research scientists collaborating with them have relied upon for almost two decades. Barring this Court's review, the Federal Circuit's opinion will be the last word on the subject. This Court should review this case to decide whether, consistent with the pervasive view before this case, Congress adopted the drug-research safe harbor to promote the development of new drugs, not just to promote generics.

APPENDIX

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

02-1052, -1065

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE,

Plaintiffs-Cross Appellants,

and

TELIOS PHARMACEUTICALS, INC.,

Plaintiff-Appellee,

v.

MERCK KGaA,

Defendant-Appellant,

and

THE SCRIPPS RESEARCH INSTITUTE and DR. DAVID A. CHERESH,

Defendants.

Donald R. Dunner, Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., of Washington, DC, argued for defendant-appellant Merck KGaA. With him on the brief were Thomas H. Jenkins, David A. Manspeizer, and Rachel H. Townsend. Of counsel on the brief were M. Patricia Thayer, Heller Ehrman White & McAuliffe, LLP, of San Francisco, California; and William C. Rooklidge, Howrey Simon Arnold & White, LLP, of Irvine, California. Of

counsel was Esther H. Lim, Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., of Washington, DC.

Mauricio A. Flores, Campbell & Flores LLP, of San Diego, California, argued for plaintiffs-cross appellants Integra LifeSciences I, Ltd. and The Burnham Institute. With him on the brief was David M. Beckwith. Of counsel on the brief were Raphael V. Lupo, Mark G. Davis, and Natalia V. Blinkova, McDermott, Will & Emery, of Washington, DC. Of counsel was Donna M. Tanguay.

Appealed from: United States District Court for the Southern District of California

Senior Judge James M. Fitzgerald, District of Alaska

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

02-1052,-1065

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE,

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v.

MERCK KGaA,

Defendant-Appellant,

and

THE SCRIPPS RESEARCH INSTITUTE and DR. DAVID A. CHERESH,

DECIDED: June 6, 2003

Before NEWMAN, RADER, and PROST, Circuit Judges.

Opinion for the court filed by Circuit Judge RADER. Concurring-in-part, dissenting-in-part opinion filed by Circuit Judge NEWMAN.

RADER, Circuit Judge.

Following a jury trial, the United States District Court for the Southern District of California ruled that Merck KgaA (Merck) infringed U.S. Patent Nos. 4,988,621 ('621 patent), 4,792,525 ('525 patent) 5,965,997 ('997 patent), 4,879,237 ('237 patent), and 4,789,734 ('734 patent), belonging to Integra Lifesciences I, Ltd., the Burnham Institute and Telios Pharmaceuticals, Inc.[1] (Integra). The district court held that subsection (e) of 35 U.S.C. § 271 did not immunize Merck against liability for infringement of the '525, '237, '997, and '734 patents. See 35 U.S.C. § 271(e)(1) (2000). The district court, however, granted Merck's motion for summary judgment of invalidity of claim 2 of the '621 patent. Integra LifeSciences I Ltd. v. Merck KGaA, 50 USPQ2d 1846, 1850, 1999 WL 398180 (S.D. Cal. 1999). The jury awarded a reasonable royalty of $15,000,000. Because the district court correctly construed the claims and determined that Merck's infringing activity did not fall within the safe harbor of § 271(e), this court affirms those aspects of the district court's order. Because substantial evidence does not support the jury's reasonable royalty award, however, this court remands for further consideration of damages.

I.

Integra owns the '621, '525, '997, '237, and '734 patents, all of which are related to a short tri-peptide segment of fibronectin having the sequence Arg-Gly-Asp (in single-letter notation, referred to as the "RGD peptide"). The RGD peptide sequence promotes cell adhesion to substrates in culture and in vivo. The RGD sequence promotes this beneficial cell adhesion by interacting with $\alpha_v\beta_3$ receptors on cell surface proteins called integrins. In sum, the RGD

[1] As of December 1996, Integra acquired all of Telios' property rights in the asserted patents.

sequence attaches to the $\alpha_v\beta_3$ receptors on the surface of cells. This bond adheres the cells to the substrate containing RGD. In theory, inducing better cell adhesion and growth should promote wound healing and biocompatibility of prosthetic devices. In addition, blood vessels grow new branches due to controlled interactions with integrins.

Dr. David Cheresh, a scientist at Scripps, discovered that blocking $\alpha_v\beta_3$ receptors inhibits angiogenesis, the process for generating new blood vessels. Inhibiting angiogenesis showed promise as a means to halt tumor growth by starving rapidly dividing tumor cells. Similarly, anti-angiogenic therapies might also treat diabetic retinopathy, rheumatoid arthritis, psoriasis, and inflammatory bowel disease.

Merck recognized the importance of Dr. Cheresh's discovery, and hired Scripps and Dr. Cheresh to identify potential drug candidates that might inhibit angiogenesis. Dr. Cheresh's research showed that cyclic peptide EMD 66203 displayed good inhibition of $\alpha_v\beta_3$ receptors. Merck then entered into an agreement with Scripps to fund the "necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials" with EMD 66203 or a derivative thereof. The agreement contemplated commencing clinical trials with a drug candidate within three years.

Scripps' research led to the discovery of EMD 85189, and then EMD 121974 - both derivatives of EMD 66203. Scripps scientists conducted several in vivo and in vitro experiments "to evaluate the specificity, efficacy, and toxicity of EMD 66203, 85189 and 121974 for various diseases, to explain the mechanism by which these drug candidates work, and to determine which candidates were effective and safe enough to warrant testing in humans." In particular, these tests assessed the action of the cyclic RGD peptides, including the histopathology, toxicology,

circulation, diffusion, and half-life of the peptides in the bloodstream. These tests also examined the proper mode of administering the peptides for optimum therapeutic effect. In 1997, the Scripps research team chose EMD 121974 as the best candidate for clinical development.

Integra learned of the Scripps-Merck agreement. Believing the angiogenesis research was a commercial project that infringed its RGD-related patents, Integra offered Merck licenses to the patents-in-suit. After lengthy negotiations, Merck declined. Integra then sued Merck, Scripps, and Dr. Cheresh. Merck answered that its work with Scripps falls under the safe harbor afforded by 35 U.S.C. § 271(e)(1). Merck also contended Integra's patents were invalid. Before trial, Integra limited its request for monetary damages to Merck's alleged infringement, and sought only a declaratory judgment against Scripps and Cheresh. After the close of all evidence, the district court granted Scripps' and Dr. Cheresh's motion to dismiss Integra's claim for declaratory judgment.

At trial, the jury found Merck liable for infringing the '525, '997, '237, and '734 patents. The district court determined that the exemption of § 271(e)(1) did not embrace the infringing activity between 1994 and 1998.[2]

[2] In her dissent, Judge Newman takes this opportunity to restate her dissatisfaction with this court's decision in Madey v. Duke. Madey v. Duke Univ., 307 F.3d 1351, 64 USPQ2d 1737 (Fed. Cir. 2002). However, the common law experimental use exception is not before the court in the instant case. The issue before the jury was whether the infringing pre-clinical experiments are immunized from liability via the "FDA exemption," i.e., 35 U.S.C. § 271(e)(1). The district court did not instruct the jury on the common law research exemption with respect to the Merck's infringing activities. On appeal, Merck does not contend that the common law research exemption should apply to any of the infringing activities evaluated by the jury. Neither party has briefed this issue to this court. Moreover, during oral arguments, counsel for Merck expressly stated that the common law research exemption is not relevant to its appeal. Judge Newman's dissent, however, does not mention that the Patent Act does not include the word "experimental," let alone an experimental use exemption from infringement. See 35 U.S.C. § 271 (2000). Nor does Judge Newman's dissent note that the judge-made doctrine is rooted in the notions of de minimis infringement better addressed by limited damages. Embrex v. Service Eng'g Corp., 216 F.3d 1343, 55 USPQ2d 1161 (Fed. Cir. 2000) (Rader, J., concurring); see also Deuterium Corp. v. United States, 19 Cl.Ct. 624, 631, 14 USPQ2d 1636, 1642 (Cl. Ct. 1990) ("This court questions whether any infringing use can be de minimis. Damages for an extremely small infringing use may be de minimis, but infringement is not a question of degree.").

The district court, however, granted Merck's summary judgment motion on claim 2 of the '621 patent. The district court invalidated this claim based on anticipation by a 1984 Nature article. The parties filed various post-trial motions. In particular, Merck filed motions for JMOL before and after jury deliberations, asserting, inter alia, that the accused experiments were exempt from infringement under 35 U.S.C. § 271(e)(1); that Integra did not prove infringement of any patents; and that substantial evidence did not support the damages award. The district court denied Merck's motions.

Merck timely appeals, asserting error in the district court's interpretation of § 271(e)(1), in claim construction, and in the refusal to reconsider the amount of the damages award. Integra cross-appeals the denial of its motion for declaratory judgment of infringement by Scripps and Dr. Cheresh, the invalidity finding on the '621 patent, and the court's refusal to enhance the damages award. This court has exclusive jurisdiction. 28 U.S.C. § 1295(a)(1) (2000).

II.

This court reviews statutory interpretation without deference. Vectra Fitness, Inc. v. TNWK Corp., 162 F.3d 1379, 1381, 49 USPQ2d 1144, 1146 (Fed. Cir. 1998). Similarly, this

court reviews claim construction without deference. Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1456, 46 USPQ2d 1169, 1172 (Fed. Cir. 1998) (en banc). Determining a reasonable royalty is an issue of fact, which this court reverses only in the absence of substantial evidence. Unisplay, S.A. v. Am. Elec. Sign Co., 69 F.3d 512, 517, 36 USPQ2d 1540, 1544 (Fed. Cir. 1995); Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1240-41, 9 USPQ2d 1913, 1924 (Fed. Cir. 1989). Finally, this court reviews the denial of JMOL following a jury verdict without deference. SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp., 225 F.3d 1349, 1354, 55 USPQ2d, 1927, 1930 (Fed. Cir. 2000).

A.

35 U.S.C. § 271(e)(1) defines a safe harbor against patent infringement:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

This provision entered title 35 in 1984 as part of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (the 1984 Act). The 1984 Act had two purposes. In the first place, the 1984 Act sought to restore patent term to pharmaceutical inventions to compensate for the often-lengthy period of pre-market testing pending regulatory approval to sell a new drug. These regulatory delays can deprive a patentee of many years of its patent's term. The second reason for the 1984 Act responded to this court's decision in Roche Products, Inc. v. Bolar Pharmaceutical Co., 733 F.2d 858, 221 USPQ 937 (Fed. Cir. 1984). Specifically, the Act sought to ensure that a patentee's rights did not de facto extend past the expiration of the patent term because a generic competitor also could not enter the market without regulatory approval. See Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 669-70 (1990). Thus, the 1984 Act permitted those competitors to conduct experiments in advance of the patent expiration as long as those activities were reasonably related to securing regulatory approval. As previously noted by this court, "[s]ection 271(e) permits premarket approval activity conducted for the sole purposes of sales after patent expiration." Hoechst-Roussel Pharms., Inc. v. Lehman, 109 F.3d 756, 763, 42 USPQ2d 1220, 1226 (Fed. Cir. 1997).

The House Committee that initiated this provision expressly described the pre-market approval activity as "a limited amount of testing so that generic manufacturers can establish the bioequivalency of a generic substitute." H.R. Rep. No. 857, at 8, reprinted in 1984 U.S.C.C.A.N. at 2692. The Committee further characterized the limits of this provision, noting that the "nature of the interference with the rights of the patent holder" would not be "substantial," but "de minimus [sic]." Id. at 2692, 2714 (stating that "all that the generic can do is test the drug for purposes of submitting data to the FDA for approval. Thus, the nature of the interference is de minimus [sic]."). Thus, the 1984 Act was "designed to benefit the makers of generic drugs, research-based pharmaceutical companies, and not incidentally the public." Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1568, 42 USPQ2d 1257, 1262 (Fed. Cir. 1997).

This court has had occasion to consider the limits of the words "solely for purposes reasonably related to the development and submission of information under a Federal law." Applying this language, this court has permitted clinical trials and demonstrations of medical devices under § 271(e)(1). See Intermedics Inc. v. Ventritex Co., 775 F. Supp. 1269 (N.D. Cal. 1991), aff'd, 991 F.2d 808, 26 USPQ2d 1524 (Fed. Cir. 1993) (citing Telectronics Pacing Sys., Inc. v. Ventritex, Inc., 982 F.2d 1520 (Fed. Cir. 1992)).

This court has not considered the question arising in this case, namely, whether the pre-clinical research conducted under the Scripps-Merck agreement is exempt from liability for infringement of Integra's patents under § 271(e)(1). The Scripps-Merck experiments did not supply information for submission to the United States Food and Drug Administration (FDA), but instead identified the best drug candidate to subject to future clinical testing under the FDA processes. Thus, this court must determine whether the § 271(e)(1) safe harbor reaches back down the chain of experimentation to embrace development and identification of new drugs that will, in turn, be subject to FDA approval.

According to 35 U.S.C. § 271(a), anyone who "without authority makes, uses, sells, or offers to sell any patented invention, within the United States during the term of the patent therefor, infringes the patent." 35 U.S.C. § 271(a) (2000). In this case, Merck used the Integra inventions, and thus infringed its patents. Merck may, nonetheless, escape liability for patent infringement if its uses of the Integra inventions fall within the strict limits of § 271(e)(1). To qualify for exemption[3], Merck must show its

[3] While the express language of § 271(e)(1) states that "it shall not be an act of infringement" to carry out research activities "solely for uses reasonably related " to FDA submissions, the statute has been coined an "exemption" in the case law, drawing from terminology used in the legislative history. See H.R Rep. No. 857, at 5, reprinted in 1984 U.S.C.C.A.N. at 2689 ("In order to facilitate this type of testing, section 202 of the bill creates general [sic] exception to the rules of patent infringement."); see also Allergan, Inc. v. Alcon Laboratories, Inc., 324 F.3d 1322, 1325-26, 66 USPQ2d 1225, 1227-28 (Fed. Cir. 2003) (discussing § 271(e)(1) as an "exemption" to patent infringement). This decision employs the same terminology.

activities were "solely for uses reasonably related to the development and submission of information" to the FDA. 35 U.S.C. § 271(e)(1).

At the outset, this statutory language strictly limits the exemption "solely" to uses with a reasonable relationship to FDA procedures. The term "solely" places a constraint on the inquiry into the limits of the exemption. The exemption cannot extend at all beyond uses with the reasonable relationship specified in § 271(e)(1).

The 1984 Act further specifies the subject of the reasonable relationship test. The exemption covers uses "reasonably related to the development and submission of information" to the FDA. Thus, to qualify at all for the exemption, an otherwise infringing activity must reasonably relate to the development and submission of information for FDA's safety and effectiveness approval processes. The focus of the entire exemption is the provision of information to the FDA. Activities that do not directly produce information for the FDA are already straining the relationship to the central purpose of the safe harbor. The term "reasonably" permits some activities that are not themselves the experiments that produce FDA information to qualify as "solely for uses reasonably related" to clinical tests for the FDA. Again, however, the statutory language limits the reach of that relationship test.

In this case, the Scripps work sponsored by Merck was not clinical testing to supply information to the FDA, but only general biomedical research to identify new pharmaceutical compounds. The FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval. For instance, the FDA does not require information about drugs other than the compound featured in an Investigational New Drug application. Thus, the Scripps work sponsored by Merck was not "solely for uses reasonably related" to clinical testing for FDA.

The reach of the reasonable relationship test as applied in this case receives further confirmation from the context of the 1984 Act. The meaning of the phrase "reasonably related to the development and submission of information" as set forth in § 271(e)(1) is clearer in the context of the role of the 1984 Act in facilitating expedited approval of a generic version of a drug previously approved by the FDA.

As discussed above, the express objective of the 1984 Act was to facilitate the immediate entry of safe, effective generic drugs into the marketplace upon expiration of a pioneer drug patent. The 1984 Act thus permits filing of an ANDA (abbreviated new drug application) to expedite FDA approval of a generic version of a drug already on the market. Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 54 USPQ2d 1711 (Fed. Cir. 2000). This expedited approval process requires the generic drug company to perform safety and effectiveness tests on its product before expiration of the patent on the pioneer drug if the generic is to be available immediately upon patent expiration. As noted, however, this court had ruled that those pre-expiration tests infringe the patent on the pioneer drug. Roche, 733 F.2d at 858. Therefore, the 1984 Act enacted § 271(e)(1) to create a safe harbor for those pre-expiration tests necessary to satisfy FDA requirements. As also noted, the legislative record shows as well that the 1984 Act narrowly tailored the

§ 271(e)(1) exemption to have only a de minimis impact on the patentee's right to exclude. Therefore, the § 271(e)(1) safe harbor covers those pre-expiration activities "reasonably related" to acquiring FDA approval of a drug already on the market. Within this framework and language of the 1984 Act, the district court correctly confined the § 271(e)(1) exemption to activity that "would contribute (relatively directly)" to information the FDA considers in approving a drug. Intermedics, 775 F. Supp. at 1280.

The exemption viewed in this context does not endorse an interpretation of § 271(e)(1) that would encompass drug development activities far beyond those necessary to acquire information for FDA approval of a patented pioneer drug already on the market. It does not, for instance, expand the phrase "reasonably related" to embrace the development of new drugs because those new products will also need FDA approval. Thus, § 271(e)(1) simply does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process. The safe harbor does not reach any exploratory research that may rationally form a predicate for future FDA clinical tests.

As noted, the text of § 271(e)(1) limits the exemption "solely" to activities "reasonably related to the development and submission of information" to the FDA. Moreover, the context of this safe harbor keys its use to facilitating expedited approval of patented pioneer drugs already on the market. Extending § 271(e)(1) to embrace new drug development activities would ignore its language and context with respect to the 1984 Act in an attempt to exonerate infringing uses only potentially related to information for FDA approval. Moreover, such an extension would not confine the scope of § 271(e)(1) to de minimis encroachment on the rights of the patentee. For example, expansion of § 271(e)(1) to include the Scripps-Merck activities would effectively vitiate the exclusive rights of patentees owning

biotechnology tool patents. After all, patented tools often facilitate general research to identify candidate drugs, as well as downstream safety-related experiments on those new drugs. Because the downstream clinical testing for FDA approval falls within the safe harbor, these patented tools would only supply some commercial benefit to the inventor when applied to general research. Thus, exaggerating § 271(e)(1) out of context would swallow the whole benefit of the Patent Act for some categories of biotechnological inventions. Needless to say, the 1984 Act was meant to reverse the effects of Roche under limited circumstances, not to deprive entire categories of inventions of patent protection.

Because the language and context of the safe harbor do not embrace the Scripps-Merck general biomedical experimentation, this court discerns no error in the district court's interpretation of 35 U.S.C. § 271(e)(1). This court affirms that aspect of the district court's decision.

B.

Merck contends that the district court erred in construing the asserted claims of the '525, '997, and '237 patents to embrace both linear and cyclic RGD peptides. Representative claim 8 of the '525 patent reads:

> A substantially pure peptide including as the cell-attachment-promoting constituent the amino acid sequence Arg-Gly-Asp-R wherein R is Ser, Cys, Thr or other amino acid, said peptide having cell-attachment-promoting activity, and said peptide not being a naturally occurring peptide.

The '237 patent claims methods of controlling Arg-Gly-Asp mediated attachments of animal cells to substrates. The '997

patent claims recite methods of altering cell attachment activity by bringing cells into contact with peptide RGDX.

In construing claim 8 of the '525 patent, the district court concluded that the claim "imposes no limitations on the three-dimensional structure of the peptides at issue." The district court found the claim's terms, in light of the specification, fully support Integra's contention that claim 8 embraces RGD peptides of any linear or cyclic structure.

Because the patents do not expressly refer to cyclic configurations, Merck would limit the term "peptide" to linear peptides. As the district court noted, however, the term "peptide" is understood in the art to represent "two or more amino acids covalently joined by peptide bonds." By this definition, the general term "peptide" encompasses peptides of differing structural forms. The '525 patent specification refers to RGD peptides as having carboxyl and amino termini without expressly discussing cyclic RGD peptide structures. However, the specification as a whole embraces the claimed RGD peptides in both cyclic and linear conformations. The preparation of cyclic peptides was well known to those of skill in the art in 1984. As the district court correctly noted, the asserted patents need not teach that which is already known. The '525 specification references a journal article authored by Merrifield, which discloses the general knowledge of skilled artisans in making cyclic peptides at the filing date of the '525 patent. '525 patent, col. 3, ll. 60-64. The record also includes a declaration from Dr. Dedhar that the Merrifield method makes cyclic peptides. Dr. Dedhar stated that a skilled artisan "would have known from reading the patent specification in 1985 that this recognition site exists on all peptides that contain the Arg-Gly-Asp sequence, including cyclic peptides or peptides containing D-form amino acids."

Merck also contends that the patent applicant, while arguing the patentability of claims to cyclic peptides in a

later-filed, unrelated application, admitted that the '525 and '997 patents do not teach cyclic peptides. Specifically, the applicant distinguished the claims of unrelated U.S. Patent No. 5,880,092 to Ruoslahti et al. (the '092 patent) over U.S. Patent No. 4,614,517 (the '517 patent), a divisional of the parent of the '525 and '997 patents. In essence, Merck would limit the reach of the '517 patent due to statements the applicant made in another patent application, not in the application leading to the '517.

The Patent and Trademark Office cited the '517 patent as prior art against the Ruoslahti '092 patent. During prosecution of the '092 patent, the applicant stated:

> The Examiner argues that the generic peptide taught by Ruoslahti et al. anticipates the claimed peptide. . . . The reference does not disclose a subgenus or species from which a subgenus of peptides can be fashioned. As a result, one skilled in the art would not immediately envisage the claimed peptide because of the very large number of peptides encompassed by the generic teaching of this reference. . . . The reference does not suggest cyclizing a peptide to conformationally stabilize it. As a result, one skilled in the art would not immediately envisage the claimed peptide because the reference does not teach a cyclic Arg-Gly-Asp peptide.

According to Merck, this statement limits the term "peptide" in the '517 patent to non-cyclic structures. In the first place, of course, the '092 patent prosecution does not directly limit the '517 patent. See Abbott Labs. v. Dey, L.P., 287 F.3d 1097, 1104-05, 62 USPQ2d 1545, 1550 (Fed. Cir. 2002) (stating that as between two patent applications sharing an inventor and the same assignee, but having no formal

relationship, "the relationship, if any, between the '839 and '301 patents is insufficient to render the particular arguments made during prosecution of the '301 patent equally applicable to the claims of the '839 patent"). Those comments arise in a context different from the patentability of the '517 patent. Moreover, the above statement loosely describes the patentee's understanding of the '517/'525/'997 specification, but does not definitively limit the scope of the Integra inventions. These comments in the '092 prosecution evince the patent applicant's understanding that the '525 specification generically teaches "a very large number of peptides." The applicant notes that one of skill in the art would not "immediately envisage" conflict with the '092 invention. This characterization does not compromise the scope of the Integra inventions. The '525 patent is a genus patent. Such genus patents do not estop the applicant from later filing an improvement patent, such as the '517, to claim species with particularly useful properties. See In re Borah, 354 F.2d 1009, 148 USPQ 213 (CCPA 1966). Accordingly, Merck's reliance on this ambiguous and unrelated prosecution history is misplaced, as it does not limit the asserted claims to linear peptides.

Thus, the specification of Integra's invention does not limit the term "peptide" to only a linear structure. As the record indicates, the patentee discloses to those skilled in the art both linear and cyclic peptides. The district court correctly construed the term to have its full ordinary meaning in the art.

C.

Following its determination of infringement, the jury awarded Integra a reasonable royalty of $15,000,000. Merck contends this award is not supported by substantial evidence. For the reasons articulated below, this court agrees.

After finding patent infringement, a jury may award a patentee "damages adequate to compensate for the infringement, but in no event less than a reasonable royalty for the use made of the invention by the infringer." 35 U.S.C. § 284 (2000). Thus, an injured patentee enjoys at least a reasonable royalty even when unable to show lost profits or an established royalty rate. A reasonable royalty calculation envisions and ascertains the results of a hypothetical negotiation between the patentee and the infringer at a time before the infringing activity began. Riles v. Shell Exploration & Prod. Co., 298 F.3d 1302, 1311, 63 USPQ2d 1819 (Fed. Cir. 2002) (citing Hanson v. Alpine Valley Ski Area, Inc., 718 F.2d 1075, 1078, 219 USPQ 679, 682 (Fed. Cir. 1983)). Thus, the reasonable royalty calculus assesses the relevant market as it would have developed before and absent the infringing activity. Although an exercise in approximation, this analysis must be based on "sound economic and factual predicates." Riles, 298 F.3d at 1311 (citing Crystal Semiconductor Corp. v. TriTech Microelectronics Int'l, Inc., 246 F.3d 1336 (Fed. Cir. 2001); Shockley v. Arcan, Inc., 248 F.3d 1349, 58 USPQ2d 1692 (Fed. Cir. 2001)). Royalties, like lost profits, are compensatory damages, not punitive. See Riles, 298 F.3d at 1312.

The first step in a reasonable royalty calculation is to ascertain the date on which the hypothetical negotiation in advance of infringement would have occurred. The correct determination of this date is essential for properly assessing damages. The value of a hypothetical license negotiated in 1994 could be drastically different from one undertaken in 1995 due to the more nascent state of the RGD peptide research in 1994. Indeed, factoring in the rapid development of biotechnological arts, a year can make a great difference in economic risks and rewards. In any event, the record is not clear on the hypothetical negotiation date.

Integra charged Merck with infringing the '525 patent by conducting various experiments between 1994 and 1998. The district court ruled that some of the 1994 experiments are not infringing acts. This finding, however, does not properly establish the critical hypothetical negotiation date. The record shows that at least one of the 1994 Merck experiments was not considered exempted from infringement due to experimental use. Integra alleged infringement via an August 1994 pharmacokinetic experiment. Merck represents to this court in its brief that the jury returned a verdict finding that "Scripps and Cheresh infringed all of the patents by conducting various experiments between 1994-98 (the 'accused experiments' or the '1994-98 experiments')." Yet, it is not evident whether the 1994 pharmacokinetic experiment was considered by the jury for infringement purposes. Thus, the record does not clearly indicate whether 1994 or 1995 is the proper date for the first infringement. If indeed the record shows that the first infringement occurred in 1994, then the hypothetical negotiation should be regarded as having occurred at least before that earlier date. On remand, the trial court will have the opportunity to clarify the proper timing of the reasonable royalty calculus.

Integra argues further that Mr. Anderson's testimony supports the $15,000,000 award. Mr. Anderson proffered a hypothetical license figure based, in part, on Merck's 1995 expectations of obtaining FDA approval of a cyclic peptide therapeutic. As already noted, however, if the hypothetical negotiation occurred in 1994, Merck did not have that expectation. Thus, an earlier date will change the risks and expectations of the parties.

Integra argues that the $15,000,000 award is not excessive because Merck and ImClone executed a license for a pre-clinical stage antibody in 1990. The ImClone license included an up-front fee of $3,500,000, plus an additional $14,000,000 over the following three years. The record is

not clear, however, that the level of risk associated with the licensed ImClone technology was equally applicable to the RGD technology. While the ImClone agreement may show that Merck pays up-front fees for research technology before clinical testing, the nature of the ImClone technology at the time of the Merck agreement may have no bearing on the value of a hypothetical RGD license. At the point before Merck ever attempted its first test on RGD technology, it would have assumed all the risks of failure – either scientific failure to identify a suitable therapeutic candidate or economic failure to market a successful product. If those risks as perceived before any experimentation differed from the risks quantified in the ImClone agreement, then the ImClone example does little to set the value of the pre-clinical RGD research project at a comparable figure. The parties' inability to project success at the pre-clinical research stage of the RGD project weighs heavily in determining a reasonable royalty, particularly if the time for the valuation of the project moves back to 1994. The record does not show that the ImClone licenses occurred under scientific or economic circumstances that permit comparison to this hypothetical RGD license.

Although comparisons to other licenses are inherently suspect because economic and scientific risks vary greatly, the record does seem to contain a more appropriate analogue than the ImClone license. In 1995, Telios and Genentech reached agreement to jointly develop and market a product with RGD peptides. This license is somewhat contemporary and involves similar technology. Under the Genentech agreement, Telios agreed to provide Genentech with exclusive patent licenses and years of research services. Under the hypothetical negotiation in this case, Integra would perform no pre-clinical research for Merck. Thus, even this analogue would need revision and inquiry.

The $15,000,000 royalty also does not appear to take into account numerous factors that would considerably

reduce the value of a hypothetical license. For example, Integra purchased Telios (together with all of its products, patents and know-how) for $20,000,000 in 1996. A $15,000,000 award figure to compensate for infringement of only some of Telios' patents before Integra's acquisition seems unbalanced in view of the overall acquisition price.

Finally, on remand, the trial court will have the opportunity to consider other factors when sketching an overall picture of a hypothetical negotiation for a license to RGD technology. The value to a licensee of research tools lies, in part, in the point at which those tools are employed in the drug development continuum. A research tool enabling the identification of a drug candidate during high throughput screening, for instance, may supply more value to the ultimate invention than a research tool used to confirm an already recognized drug candidate's safety or efficacy. This type of challenge in assessing royalties confronted the district court in SIBIA, although this court never reached the issue of damages on appeal. See SIBIA, 225 F.3d at 1349, 1352-53; see also Donald Ware, Research Tool Patents: Judicial Remedies, 30 AIPLA Q.J., 267, 282-87 (2002). Similarly, the amount Merck would agree to pay for Integra's RGD technology could be influenced by the point of placement of this technology in its drug development process.

In addition, the number of patent licenses needed to develop a drug may also affect the value placed on any single technology used in the development process. The cumulative effect of such stacking royalties can be substantial, particularly when reach-through royalties come into play. See Ware, supra, at 295-96. While this court does not opine on the applicability of a reach-through royalty in this case, the presence or absence of stacking royalties for research tools may color the character of a hypothetical

negotiation between Merck and Integra for access to the RGD peptide technology.[4] Thus, both the time point at which Merck utilized RGD peptides in its drug development process and the effect, if any, of stacking royalties may also play a role in crafting the hypothetical license between Integra and Merck.

This court gives great deference to the district court's role in assessing the credibility of witnesses and weighing the facts of a given case. Nonetheless, the record evidence does not adequately support the jury's damage award of $15,000,000 in this case. Therefore, the district court's denial of JMOL as to the damage award is reversed. This case is remanded for further factual development and the calculation of damages consistent with the principles discussed herein.

D.

All other arguments made by the parties have been carefully considered, but are not found persuasive by this

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[4] According to the National Institutes of Health (NIH), research tools are defined to be "tools that scientists use in the laboratory, including cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry and DNA librarie. clones and cloning tools (such as PCR), methods, laboratory equipment and machines." Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts, 64 Fed. Reg. 72,090, 72092 n.1 (Dec. 23, 1999). The dissent asserts that Integra's patented RGD peptides are not research tools, "but simply new compositions having certain uses." Dissent at Section D. The dissent does not explain why one of those "certain uses" cannot embrace use of an RGD peptide as a laboratory tool to facilitate the identification of a new therapeutic. Regardless of whether one considers the RGD peptides to assume the label of a "research tool," the points discussed in relation to determining the value of the peptides during a hypothetical negotiation are valid.

court. Thus, this court affirms the district court's denial of Integra's request for declaratory judgment, its holding that the '621 patent is invalid, and its refusal to grant enhanced damages.

CONCLUSIONS

Because the district court properly determined Merck's infringing activities were not "solely for uses reasonably related" to provision of information to the FDA under 35 U.S.C. § 271(e)(1), this court affirms that aspect of the district court's decision. In addition, the district court correctly construed the term "peptide" to have its full ordinary meaning in the art. However, the district court erred in denying Merck's motion for reconsideration of an appropriate reasonable royalty. Therefore, the court remands for further consideration of the damages issue.

COSTS

Each party shall bear its own costs.

AFFIRMED-IN-PART, REVERSED-IN-PART, and REMANDED

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRUIT

INTEGRA LIFESCIENCES I, LTD. and
THE BURNHAM INSTITUTE,

Plaintiffs-Cross Appellants,

and

TELIOS PHARMACEUTICALS, INC.,

Plaintiff-Appellee,

v.

MERCK KGaA,

Defendant-Appellant,

and

THE SCRIPPS RESEARCH INSTITUTE and
DR. DAVID A. CHERESH,

Defendants.

NEWMAN, Circuit Judge, concurring in part, dissenting in part.

This case raises a question of the nature and application of the common law research exemption, an exemption from infringement that arose in judge-made law almost two centuries ago, and that recently has come into sharper focus. Its correct treatment can affect research institutions, research-dependent industry, and scientific progress.

The question is whether, and to what extent, the patentee's permission is required in order to study that which is patented. For the Scripps/Merck research, the panel majority holds that all of the activity at Scripps during 1995-1998 was "discovery-based research" and that there is no right to conduct such research, under either the common law research exemption or the statutory immunity established in 35 U.S.C. §271(e)(1). However, neither law nor policy requires that conclusion, and both law and policy have long required a different conclusion in implementation of the purpose of the patent system.

The purpose of a patent system is not only to provide a financial incentive to create new knowledge and bring it to public benefit through new products; it also serves to add to the body of published scientific/technologic knowledge. The requirement of disclosure of the details of patented inventions facilitates further knowledge and understanding of what was done by the patentee, and may lead to further technologic advance. The right to conduct research to achieve such knowledge need not, and should not, await expiration of the patent. That is not the law, and it would be a practice impossible to administer. Yet today the court disapproves and essentially eliminates the common law research exemption. This change of law is ill-suited to today's research-founded, technology-based economy. I must, respectfully, dissent.

A. The Scripps/Merck Activities

The research on which Scripps and Merck collaborated was directed to studies of certain peptide components of fibronectin, containing a chain of the three amino acids arginine (R), glycine (G), and aspartic acid (D). The scientists who founded Integra's predecessor, co-plaintiff Telios, discovered that peptides containing this RGD sequence had potential use in promoting wound healing and prosthesis adhesion, and obtained patents on various RGD

peptide compositions and methods; however, the Telios scientists were unable to develop a viable commercial product, and eventually sold the patents to Integra.

Merck KGaA of Germany began funding research at Scripps in 1988, after Dr. Cheresh of Scripps had identified a monoclonal antibody, designated LM609, having activity as an inhibitor of integrin[1] activity. The collaboration was enlarged in 1995 with increased funding by Merck, after Dr. Cheresh discovered that a Merck-provided peptide designated EMD66203, having the sequence c(RGDfV),[2] inhibits new blood vessel growth by interaction with a specific integrin. In this collaboration, cyclic RGD peptides of various structures and composition[3] were synthesized and studied, as knowledge was gained concerning their chemical and biological properties and the effects of changes in their structure. It was discovered that the cyclic peptide structure solved certain problems that had been experienced with the Telios linear RGD peptides, and that some products have anti-angiogenic properties, of interest for treatment of such diseases as cancer, macular degeneration, rheumatoid arthritis, and others. "Angiogenic" refers to the process of generating new blood vessels, a process essential to tumor

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1 "Integrin" refers to a family of cell surface receptors.

2 In this nomenclature L isomers of amino acids are represented by their single letter codes in capital letters (R=arginine, G=glycine, D=aspartic acid). The "f" represents the D isomer of phenylalanine. "NMeV," appearing infra, represents the N-methyl derivative of valine. The "c" means that the sequence is cyclic.

3 Also at issue in this litigation was whether the Integra patents cover the cyclic RGD peptides that were produced and investigated by Scripps/Merck. On this close question of infringement I would affirm the district court, as does the panel majority, for there was extensive evidence at trial, including the (conflicting) advice of experts, supporting the district court's findings.

growth. As summarized by Merck, Dr. Cheresh testified that the purpose of the research was to "(1) assess the potential efficacy of the peptides as therapeutic agents; (2) discover the mechanism of action of the peptides; and (3) shed light on histopathology, toxicology, circulation, diffusion, and half-life of the peptides in the bloodstream." Brief at 15. The ultimate goal of the research was undisputed: it was to find a product that would be sufficiently effective in the treatment of angiogenic disease that it could be developed and brought to market for this purpose.

The record describes modifications in the structure of RGD-containing peptides and investigations of their properties in the Scripps/Merck collaboration, including: receptor binding assays to investigate the efficacy and specificity of structural change; angiogenesis/chick CAM assays for inhibition of blood vessel formation in chick embryos when vessel growth is artificially induced, to study the mechanism of action, pharmacokinetics, and other properties; angio-matrigel experiments to investigate inhibition of artificially induced vascularization in mice; cell adhesion assays by spectrophotometric measurement of inhibition of cell attachment to protein, to provide information about mechanisms, efficacy, and other properties; chemotaxis studies to determine the effect of various peptides on cell migration over extracellular matrix fibers; use of chick embryos to obtain pharmacokinetic data; fluorescent-activated cell sorting to study the effect on the receptor-ligand binding reaction, to aid in understanding mechanisms of activity; vascularization of the retina and induced arthritis of the joints, studied with mice and rabbits; chick CAM assays to study angiogenesis associated with tumor transplantation and growth in chick embryos; and tumor growth in SCID-mice or nude mice, including studies of mechanism, pharmacology, and pharmacokinetics.

As this research progressed, so did the scientific understanding of these peptide products and their mode of

action. In 1997 Scripps/Merck selected the peptide designated EMD 121974 and having the amino acid sequence c(RGDf-NMeV) as the most promising product thus far, although they continued to synthesize and evaluate further modifications of the peptides. In 1998 an Investigatory New Drug application for EMD 121974 was filed with the Food and Drug Administration.

The panel majority describes all of this activity as "discovery-based research," and holds that it is subject to neither a common law research exemption nor the "safe harbor" of §271(e)(1). I cannot agree. In my view, either the common law research exemption or the development associated with §271(e)(1) immunity embraces all of these activities.

B. The Common Law Research Exemption

The common law research exemption is a limited exception to the patentee's unrestricted right to exclude. Its jurisprudential origin is with Justice Story, who stated in Whittemore v. Cutter, 29 Fed. Cas. 1120, 1121 (C.C.D. Mass. 1813) (No. 17,600), that

> it could never have been the intention of the legislature to punish a man who constructed such a machine merely for philosophical experiments,[4] or for the purpose of ascertaining the sufficiency of the machine to produce its described effects.

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[4] By "philosophical" experiments Justice Story was referring to "natural philosophy," the term then used for what we today call "science." For example, in the volume on Classification of Subjects of Inventions Adopted by the United States Patent Office, January 1, 1868 (GPO 1868), the section headed "Philosophical Instruments -- Class XXV" lists "Philosophical Apparatus, Scales, Measures, and Instruments of Precision."

Again in Sawin v. Guild, 21 Fed. Cas. 554 (C.C.D. Mass. 1813) (No. 12,391) Justice Story distinguished

> the making with an intent to use for profit, and not for the mere purpose of philosophical experiment, or to ascertain the verity and exactness of the specification.

The few judicial decisions on this issue have applied the research exemption when no commercial purpose was demonstrated for the research. See, e.g., Chesterfield v. United States, 159 F. Supp. 371 (Ct. Cl. 1958) (experimentation by the United States did not infringe the patent); Ruth v. Stearns-Roger Manufacturing Co., 13 F. Supp. 697 (D. Colo. 1935) (patent not infringed when the Colorado School of Mines cut up and studied the patented machines).

The majority's prohibition of all research into patented subject matter is as impractical as it is incorrect. The information contained in patents is a major source of scientific as well as technologic knowledge. Indeed, in many areas of technology, technical information is not published outside of patent documents. A rule that this information cannot be investigated without permission of the patentee is belied by the routine appearance of improvements on patented subject matter, as well as the rapid evolution of improvements on concepts that are patented.

The subject matter of patents may be studied in order to understand it, or to improve upon it, or to find a new use for it, or to modify or "design around" it. Were such research subject to prohibition by the patentee the advancement of technology would stop, for the first patentee in the field could bar not only patent-protected competition, but all research that might lead to such competition, as well as barring improvement or challenge or avoidance of

patented technology. Today's accelerated technological advance is based in large part on knowledge of the details of patented inventions and how they are made and used. Prohibition of research into such knowledge cannot be squared with the framework of the patent law.

The patent statute requires full disclosure of the invention, including details of enabling experiments and technical drawings and best modes and preferred embodiments, even commercial sources of special components. Such details would be idle and purposeless if this information cannot be used for 17-20 years. Indeed, there would be little value in the requirement of the patent law that patented information must be removed from secrecy in consideration of the patent right to exclude, if the information is then placed on ice and protected from further study and research investigation. To the contrary, the patent system both contemplates and facilitates research into patented subject matter, whether the purpose is scientific understanding or evaluation or comparison or improvement. Such activities are integral to the advance of technology.

In the framework of United States patent law there is no obligation that the patentee use the invention; the obligation is to disclose it and describe it and to provide enabling detail whereby it can be duplicated without undue experimentation. The patentee's permission is not required whenever a patented device or molecule is made or modified or investigated. Study of patented information is essential to the creation of new knowledge, thereby achieving further scientific and technologic progress.

Of course, the common law exemption is not unlimited. Indeed, it is a narrow exemption, for it must preserve the patentee's incentive to innovate, an incentive secured only by the right to exclude. It is the patentee who opened the door by providing the initial knowledge, without which there would be nothing to improve. Setting the

boundaries of a common law exemption requires careful understanding of the mechanisms of the creation, development, and use of technical knowledge, and of today's complexity of interactions among invention and the innovating fruits of invention. It is the initial inventor whose rights must receive primary consideration in an effective patent law, for the public interest starts with the threshold invention. However, while that threshold invention may (as here) exact tribute from or enjoin commercial and pre-commercial activity, the patent does not bar all research that precedes such activity.

I do not here undertake to define the boundaries of the research exemption for all purposes and all activities, other than to observe that there is a generally recognized distinction between "research" and "development," as a matter of scale, creativity, resource allocation, and often the level of scientific/engineering skill needed for the project; this distinction may serve as a useful divider, applicable in most situations. Like "fair use" in copyright law,[5] the great variety of possible facts may occasionally raise dispute as to particular cases. However, also like fair use, in most cases it will be clear whether the exemption applies. Indeed, the question of boundary does not arise for the Scripps/Merck research here at issue, for the statutory immunity of §271(e)(1) takes effect wherever the research exemption ends, as I discuss in Part C, post.

The Scripps/Merck activities that are here challenged took place during the collaboration outlined in Part A ante.

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[5] The research exemption has been compared to "fair use," which was also a creation of Justice Story, in Folsom v. Marsh, 9 Fed. Cas. 342 (C.C.D. Mass. 1841) (No. 4901). The House Report drew this analogy in discussing 35 U.S.C. §271(e)(1), stating: "Just as we have recognized the doctrine of fair use in copyright, it is appropriate to create a similar mechanism in the patent law. That is all this bill does." H.R. Rep. No. 98-857 at 30 (1984), reprinted in 1984 USCCAN 2714.

Were all research using RGD peptides prohibited until the Integra/Telios patents expired, not even the patent owner would benefit, for the patented products had failed in Telios' hands, leaving the patents valueless until Scripps and Merck made their discoveries as to the cyclic peptides and their anti-angiogenic properties. The panel majority states that because the Scripps/Merck research had the goal of curing cancer and commercializing the cure, this purpose moved the research outside of any common law exemption. However, an ultimate goal or hope of profit from successful research should not eliminate the exemption. The better rule is to recognize the exemption for research conducted in order to understand or improve upon or modify the patented subject matter, whatever the ultimate goal. That is how the patent system has always worked: the patent is infringed by and bars activity associated with development and commercialization of infringing subject matter, but the research itself is not prohibited, nor is comparison of the patented subject matter with improved technology or with designs whose purpose is to avoid the patent.

C. Immunity Under §271(e)(1); Damages

> §271(e)(1). It shall not be an act of infringement to make, use, [sell or import]. . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

The panel majority holds that the 35 U.S.C. §271(e)(1) "safe harbor" does not apply to federal registration of pioneering new drugs like the Scripps/Merck products here at issue, but only to registration of generic copies of drugs for which the patent is about to expire. I agree as to the origin of §271(e)(1). However, the statute has been interpreted as of broader scope, see Eli Lilly & Co. v. Medtronics Co., 496

U.S. 661 (1990), and the parties accept that §271(e)(1) applies to Merck's filing of the Investigatory New Drug application for EMD 121974. This issue was not raised at trial.

The majority also holds that none of the research by Scripps/Merck qualifies for §271(e)(1) immunity because the research was directed to "discovery," not to federal registration. I agree that "the §271(e)(1) safe harbor [does not] reach back down the chain of experimentation to embrace development and identification of new drugs." Maj. op. at 8. However, the territory that the Scripps/Merck research traversed, from laboratory experimentation to development of data for submission to the FDA, was either exempt exploratory research, or was immunized by §271(e)(1). It would be strange to create an intervening kind of limbo, between exploratory research subject to exemption, and the FDA statutory immunity, where the patent is infringed and the activity can be prohibited. That would defeat the purposes of both exemptions; the law does not favor such an illogical outcome.

After a product loses the §271(e)(1) protection, it is subject to the full force of any adversely held patents. That aspect is not here in dispute, but it is relevant to the damages verdict, not appropriately treated in the majority opinion.

If the question of damages is remanded, as the panel majority holds, my colleagues go too far in counseling the parties as to how to present their case. The "hypothetical negotiation" is no more than a convenience in estimating value, not a compulsory economic standard, and surely not one that requires appellate speculation as to when the parties might have hypothetically negotiated, requiring retrial. The presentation of evidence on damages was extensive, and included evidence that well supported a jury verdict that included a license. Our appellate role is to decide whether the jury verdict was supported by substantial evidence as

presented at trial, not to rewrite the trial script as we might have tuned it to our taste. See Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1570, 24 USPQ2d 1401, 1411 (Fed. Cir. 1992) (when there is sufficient evidence to support the jury verdict in light of the entire record, the verdict must stand unless the evidence permits only one reasonable conclusion.) The damages verdict is readily sustainable if construed to include a license for the remaining two to three years of patent life. The evidence before the jury well supports the magnitude of the damages award. I would affirm the verdict on that basis.

D. The Research Exemption and Research Tools

The panel majority states that acceptance of a common law research exemption would eliminate patents on "research tools." That is a misperception. There is a fundametal distinction between research into the science and technology disclosed in patents, and the use in research of patented products or methods, the so-called "research tools."

A research tool is a product or method whose purpose is use in the conduct of research, whether the tool is an analytical balance, an assay kit, a laser device (as in Madey v. Duke University),[6] or a biochemical method such as the PCR (polymerase chain reaction). It is as subject to the patent right as is any other device or method, whether it is

[6] Madey v. Duke University, 307 F.3d 1351 (Fed. Cir. 2002) concerned the use of a patented laser device for the purpose for which it was made, not research into understanding or improving the design or operation of the machine. The facts of Madey v. Duke do not invoke the common law research exemption, despite the broad statement in that opinion. I do not disagree with that decision on its facts; I disagree only with its sweeping dictum, and its failure to distinguish between investigation into patented things, as has always been permitted, and investigation using patented things, as has never been permitted.

used to conduct research or for any other purpose. Use of an existing tool in one's research is quite different from study of the tool itself.

My colleagues on this panel appear to view the Integra patents as for a "research tool." That is a misdefinition. The RGD-containing peptides of the Integra patents are not a "tool" used in research, but simply new compositions having certain biological properties. The Scripps/Merck syntheses and evaluations of new RGD peptides were not use of the Integra products as a research tool.

The majority states that this issue is not before us, that "the district court did not instruct the jury" on the question. However, the question was before the district court, who held that the common law exemption applied to one Scripps experiment in 1994, but to nothing else. The issue was before the district court, and counsel explained at oral argument that they were not pressing this argument "in part because of a very recent case." Since the question was fundamental to resolution of this case, it cannot be ignored.

Conclusion

I do not attempt to resolve, for all technologies and circumstances, the application of the research exemption or the point at which research into patented technology loses the immunity that the common law has always provided. However, the basic research here performed was within the common law research exemption, and the development shielded by §271(e)(1) took up where the research exemption left off. Thus the accused activities were either exempt from or immune from infringement.

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

ERRATA

December 3, 2003

Integra Lifesciences I, Ltd. v Merck KgaA,
Nos. 02-1052,-1605

Precedential Opinion

Decided: June 6, 2003

Page 10, line 19: insert "clearly" after "harbor" and before "covers" *[13a. line 3]

Page 10, line 21: after "the market." and before "Within this" insert the following sentence: "While the scope of the safe harbor is not limited to generic drug approval, Eli Lilly & Co. v. Medtronics Co., 496o U.S. 661 (1990), the history of the 1984 Act informs the breadth of the statutory test." [13a, line 5]

Page 11, line 7: after "embrace" and before "the development" insert "all stages of" [13a, lines 16-17]

Page 11, line 7: after "drugs" and before "because" insert "merely" [13a, line 17]

Page 11, line 10: after "form" and before "a" insert "only" [13a, line 22]

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* Page and line numbers in brackets refer to this Appendix to Merck's Petition for Writ of Certiorari.

Page 11, lines 14-15: replace "Moreover, the context of this safe harbor keys its use" with "Moreover, the context of this safe harbor originally keyed its use" [13a, lines 26-27]

Page 11, line 15: after "embrace" insert "all aspects of" [13a, line 29]

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

INTEGRA LIFESCIENCES I, LTD., a Delaware Corporation, and THE BURNHAM INSTITUTE, a California nonprofit corporation, Plaintiffs, v. MERCK KGaA, a German, corporation, Defendant.	Civil Action No. 96CV-1307 JMF

ORDER

Plaintiffs have filed a motion requesting an enhancement of damages, prejudgment interest, attorneys' fees, and an injunction against defendant. The motion has been fully briefed and oral argument has been heard.

Enhancement of Damages

The jury in this case awarded $15 million in damages and found that defendant willfully induced infringement of plaintiffs' patents. Plaintiffs request that the $15 million damage award be trebled to $45 million in order to punish and deter defendant and to send a warning to other large pharmaceutical companies who are tempted to infringe patent rights held by small companies.

The decision to increase damages is committed to the trial judge's broad discretion. Odetics, Inc. v. Storage Technologies Corp., 185 F.3d 1259, 1274 (Fed. Cir. 1999) (citations omitted). Additionally, "[t]he paramount

determination...is the egregiousness of the defendant's conduct based on all the facts and circumstances." Cybor Corp. v. FAS Technologies, Inc., 138 F.3d 1448, 1461 (Fed. Cir. 1998) (citations omitted).

In my view, the paramount issue is whether defendant's behavior constituted acts of infringement under the FDA Exemption. At trial, the jury received an instruction regarding the defense of non-infringment under 35 U.S.C. sec. 271(c):

> Merck contends that it does not infringe or induce the infringement of any of the patents-in-suit, based upon the Food and Drug Administration, or "FDA" Exemption. To prevail on this defense, Merck must prove by a preponderance of the evidence that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question.
>
> Each of the accused activities must be evaluated separately to determine whether the exemption applies.
>
> Merck does not need to show that the information gathered from a particular activity was actually submitted to the FDA.

Jury Instruction No. 32.

The above jury instruction required the jury to objectively consider whether the nature of the experimental

work undertaken and ask whether a reasonable scientist would consider that type of activity the sort likely to lead to generating data for submission to the FDA.

I conclude that the FDA Exemption is written in terms which make it difficult for a scientist to know when he or she is or is not within the exemption. Although the jury found willfulness, I find and conclude that the evidence regarding willfulness, when considered in light of the terms of the exemption, presented a "close question." The evidence revealed that defendant conducted scientific research, but did not sell any infringing products. Additionally, I find that the much of the evidence at trial established that the accused experiments generated the types of information that are submitted to the FDA. Thus, the closeness of the infringement and willfulness issues, coupled with the nebulous state of the law, creates circumstances in which it is inappropriate to enhance damages. See Modine Mfg. Co. v. Allen Group, Inc., 917 F.2d 538, 543 (Fed. Cir. 1990) (A finding of willful infringement authorizes but does not require enchancement of damages.) See also Laitram Corp. v. NEC Corp., 115 F.3d 947, 955 (Fed. Cir. 1997) (denial of enhancement of damages affirmed due to closeness of infringement and willfulness issues); Brooktree Corp. v. Advanced Micro Devices, 977 F.2d 1555, 1581-82 (Fed. Cir. 1992) (denial of enhanced damages affirmed despite jury finding of willfulness).

Request for Attorneys' Fees

An award of attorneys' fees requires a threshold determination that this is an exceptional case. 35 U.S.C. sec. 285. "The trial judge's discretion in the award of attorney fees permits the judge to weigh intangible as well as tangible factors: the degree of culpability of the infringer, the closeness of the question, litigation behavior, and any other factors whereby fee shifting may serve as an instrument of justice." Virginia Panel Corp. v. MAC Panel Co., 133 F.3d

860, 867 (Fed Cir. 1997) (citation omitted). Where a trial judge denies attorney fees in spite of a finding of willfulness, the court must explain why the case is not "exceptional." Id. As noted in Virginia Panel, "[w]illfulness in infringement...is not an-all or-nothing trait, but one of degree. It recognizes that the infringement may range from unknowing, or accidental, to deliberate, or reckless, disregard of a patentee's legal rights." Id. at n.4 (citation omitted).

As discuss above, I conclude that the defendant's infringement was neither recklessly indifferent nor deliberate. The court further concludes that defendant conducted at least a marginally sufficient investigation of the asserted patents, and defendant's behavior during the litigation was not unaceptable [sic]. Id. This was a close case which simply did not present circumstances in which defendant acted in bad faith, committed fraud, or exhibited unconscionable conduct. Accordingly, I conclude that this case is not exceptional and reject an award of attorneys' fees.

Prejudgment Interest

Prejudgment interest in a patent law case should ordinarily be awarded. See General Motors Corp. v. Devex Corp., 461 U.S. 648, 655 (1983). The purpose of prejudgment interest is to "afford patent owners complete compensation." Id.

Plaintiffs originally requested prejudgment interest in the amount of $2,820,000. Defendant did not raise an argument regarding the methodology nor rate of interest, but argued that prejudgment interest should be calculated from the date that payments would have first been received. Defendant suggests that "the Court should calculate prejudgment interest from the point of Merck's filing of and [sic] IND or an equivalent, and not from September 1995

forward." Merck's opposition to prejudgment interest at 20 n. 18.

In their reply, plaintiffs recalculate their prejudgment interest from February 1, 1998, the commencement of the European Clinical trials. Plaintiffs request prejudgment interest in the amount of $1.125 million. Plaintiffs' reply regarding prejudgment interest, Anderson reply declaration, para 2.

I find that prejudgment interest is necessary to make plaintiffs' [sic] whole, and awards [sic] prejudgment interest in the amount of $1.125 million.

Injunction

The district court is authorized to "grant injunctions in accordances with principles of equity to prevent the violation of any right secured by patent, on such terms as the court deems reasonable." 35 U.S.C. sec. 283.

Plaintiffs request that defendant be enjoined from selling EMD 66203, EMD 85189, and EMD 121974 in the United States without a license from plaintiffs. Plaintiffs do not seek to prevent Merck from making or using EMD 121974 in the United States in connection with human clinical trials. The proposed injunction would continue until November 7, 2006, the latest expiration date of the patents-in-suit.

Plaintiffs argue that without an injunction, they would be forced to institute an entirely new action to prevent defendant from selling an RGD compound that the jury found to be infringing. Ultimately, plaintiffs argue that the court should exercise its discretion and enter an injunction that will force Merck to do what its own damages expert testified defendant would do: negotiate with plaintiffs for a license to sell EMD 121974 in the United States at the point

in time defendant has obtained approval from the FDA to do so.

Defendant argues that an injunction would give plaintiffs a double recovery. Defendant argues that the damages awarded by the jury are based on calculations that take into account any potential future royalties. Defendant argues that where a jury awards lump-sum damages for use of a plaintiff's patents – that is, where it awards a flat amount for a fully paid-up license-enjoining further use of the patents would be unjustified. Trans World Mfg. Corp. v. Al Nyman & Sons, Inc., 750 F.2d 1552, 1565 (Fed. Cir. 1984)

I reject defendant's argument that the jury verdict includes post-judgment activities. The court sustained defendant's objection to Dr. Anderson expressing any opinion regarding the amount of damages that would accrue based on post-judgment activities. The court specifically stated: "I will exclude the post-judgment damages." Trial Transcript at 1326:25. Plaintiff argues that the [sic] informed the court at trial that they would seek injunctive relief only if defendant prevailed in the argument that "compensation based on post-trial events is too speculative." Plaintiffs argue that this is precisely what happened at trial when the court sustained defendant's objection and excluded post-judgment damages.

At this juncture, I conclude that it would be inappropriate to issue an injunction. The patent statute precludes issuance of an injunction unless the conduct sought to be enjoined has been determined to be protected under the FDA Exemption. 35 U.S.C. sec. 271(e)(3); Eli Lilly & Co. v. Medtronic, Inc., 915 F.2d 670, 674 (Fed. Cir. 1990) ("no injunction may issue until the section 271(e)(1) exception had been adjudicated an [sic] ruled out") *superseded by statute on other grounds*. Rotec Industries Inc. v. Mitsubishi Corp., 2000 WL 760361 (Fed. Cir. June 13, 2000). Here, no determination has been made that any

such prospective sales of Emd [sic] 66203, EMD 85189, and EMD 121974, are not subject to the FDA Exemption. At this point, I conclude that an injunction would be premature and I deny the injunction.

Summary

Plaintiffs' request for enhanced damages is denied. Plaintiffs' request for attorneys' fees is denied. Plaintiffs' request for prejudgment interest is granted in the amount of $1.125 million. Plaintiffs' request for an injunction is denied.

Dated this 19th day of July, 2000

s/ James M. Fitzgerald
Senior United States District Judge

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

INTEGRA LIFESCIENCES I, LTD., a Delaware Corporation, and THE BURNHAM INSTITUTE, a California nonprofit corporation,	)	Civil Action No. 961307 JMF
Plaintiffs,	)	
v.	)	
MERCK KGaA, a German corporation. THE SCRIPPS RESEARCH INSTITUTE, a California nonprofit corporation, DR. DAVID A. CHERESH, a California citizen, and DOES 1-25 inclusive,	)	
Defendants.	)	

Amended Judgment[1]

Judgment is entered in favor of plaintiff and against defendant Merck KGaA as follows:

1. The Scripps Research Institute and/or Dr. Cheresh have infringed United States Patent No. 4,792,525, Claim 8; nited States Patent No. 4,879,237, Claims 4 and 8; United States Patent No. 5,695,997, Claims 15, 16, 17, and 18; and United States Patent No. 4,789,734, Claim 1.

2. Defendant Merck KGaA infringed United States Patent No. 4,792,525 by importing into the United

[1] The judgment is amended to correct a typographical error in paragraph 6.

States after January 1, 1996, peptides which infringe Claim 8 of United States Patent No. 4,792,525.

3. Defendant Merck KGaA has induced infringement of United States Patent No. 4,792,525, Claim 8; United States Patent No. 4,879,237, Claims 4 and 8; United States Patent No. 5,695,997, Claims 15, 16, 17, and 18; and United States Patent No. 4,789,734, Claim 1.

4. Claim 8 of United States Patent No. 4,792,525 has not been proven invalid. Claim 1 of United States Patent No. 4,789,734 has not been proven invalid. Claims 4 and 8 of United States Patent No. 4,879,237 have not been proven invalid. Claims 15, 16, 17, and 18 of United States Patent No. 5,695,997 have not been proven invalid.

5. Plaintiffs are entitled to recover from Merck KGaA $15,000,000 in damages to compensate plaintiffs for Merck's infringement and inducing infringement.

6. Plaintiffs are entitled to recover against Merck KGaA prejudgment interest through April 30, 2000, in the amount of $1,125,000, with further prejudgment interest accruing from April 30, 2000 computed by the formula $(16{,}125.000 \times 1.0000877^{y}) - 16{,}125{,}000$ where y is the number of days from April 30, 2000 to the entry of judgment, and post judgment interest from the date of entry of this judgment until paid.

Date: October 6, 2000

s/ James M. Fitzgerald
Senior United States District Judge

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

INTEGRA LIFESCIENCES I, LTD., a Delaware Corporation, and THE BURNHAM INSTITUTE, a California nonprofit corporation,	)	No. 96CV-1307 JMF
Plaintiffs,	)	
v.	)	
MERCK KGaA, a German corporation,	)	
Defendant.	)	

Order[1]

Defendant Merck has filed a motion for judgment as a matter of law on the FDA exemption, 35 U.S.C. § 271 (e)(1). Plaintiffs oppose the motion and Merck has replied.

Merck argues that at trial, plaintiffs accused Dr. Cheresh and The Scripps Research Institute of infringing their patents by conducting sixteen categories of experiments, and accused Merck of inducing the infringement. Merck argues that the evidence presented clearly showed that the accused experiments reasonably related to generating the sorts of information likely to be relevant to the FDA regulatory process, which should have led to the conclusion that the experiments were protected under the FDA exemption.

[1] This order disposes of Post-Judgment No. 1 of 6.

"A motion for judgment as a matter of law will be granted only if the verdict is against the great weight of the evidence, or it is quite clear that the jury has reached a seriously erroneous result." Equal Employment Opportunity Commission v. Pape Liff, Inc. 115 F.3d 676, 680 (9th Cir. 1997) (citations and internal quotations omitted). The court must view the evidence in the light most favorable to the prevailing party. Landes Constr. Co. v. Royal Bank of Canada, 833 F.2d 1365, 1371 (9th Cir. 1987).

The court has reviewed the evidence and finds that it is sufficient to uphold the verdict. Plaintiffs FDA expert, Gerald Meyer, explained that the purpose of an IND application is to provide the FDA with the substantiation of safety before a drug is given to humans, and that animal data from a species is used to substantiate safety before the drug is given to humans. Meyer stated that data generated from chicken embryos is not relevant to the FDA process because it lacks an established relationship to human safety. Meyer stated further that to establish safety the FDA relies upon in vivo testing in appropriate animal models, not in vitro testing.

Merck's witnesses testified that toxicology studies must be carried out in accordance with Good Laboratory Practices (GLP), using compounds manufactured in accordance with Good Manufacturing Practices (GMP). However, Dr. Friedlander from Scripps stated that his laboratory did not comply with GLP. Additionally, Dr. Cheresh's laboratory was not GLP certified and he did not use GMP certified compounds.

Merck argues that Dr. Cheresh's experiments were relevant to establishing pharmacology and pharmacokinetics necessary for FDA approval. However, Dr. Grim, the Merck scientist responsible for preparing Merck's FDA submission, testified that side effect pharmacology testing and

pharmacokinetic tests were not performed at the Scripps Research Institute.

Merck's witness, Dr. Jonczyk admitted that Merck's infringing activity was not necessary in order to carry out any preclinical work required for Merck's RGD peptides. When asked if the work done by Scripps pursuant to the cooperative agreement with Merck comparing RGD peptides and nonpeptide inhibitors was necessary to carry out the preclinical work required for the development project on EMD 121974 and 85189 compounds, Dr. Jonczyk answered "[n]o, it is not necessary to make such a comparison." Jonczyk Trial Testimony of Feb. 23, 2000 at 97:5-20. Plaintiffs' FDA expert subsequently confirmed that the FDA does not want or required data on a search for a better compound. Trial Transcript at 3175:1-8.

Merck argues that it is entitled to judgment as a matter of law because it put some of Dr. Cheresh's data on Merck's internal computer system - the MEDIS system. Yet these actions by Merck took place after the lawsuit was filed, and Merck witnesses stated that the data on the MEDIS system did not include in vitro data. The MEDIS computer-generated time line also shows that the preclinical phase of the Merck drug development program did not commence until 1997.

The jury is entitled to make credibility decisions, and the evidence provides sufficient grounds for the jury to disregard as not credible Dr. Cheresh's testimony that the infringing experiments performed at Scripps were done for FDA purposes. Considered as a whole, the evidence is sufficient to establish that Merck, and not Dr. Cheresh or any other Scripps scientist, was responsible for conducting FDA related experiments, and that any connection between the infringing Scripps experiments and FDA review was insufficiently direct to qualify for the exam.

Considering the jury's right to weigh the evidence and determine the credibility of the witness, the evidence, when viewed in the light most favorable to plaintiffs, was sufficient for the jury to have returned a verdict in plaintiffs' favor. Merck's motion for judgment as a matter of law is denied.

Date: March 6, 2001

s/ James M. Fitzgerald
Senior United States District Judge

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

INTEGRA LIFESCIENCES I, LTD., a Delaware Corporation, and THE BURNHAM INSTITUTE, a California nonprofit corporation,	)	Civil Action No. 961307 JMF
Plaintiffs,	)	
v.	)	
MERCK KGaA, a German, corporation,	)	
Defendant.	)	

Seconded Amended Judgment

Judgment is entered in favor of plaintiff and against defendant Merck KGaA as follows:

1. The Scripps Research Institute and/or Dr. Cheresh have infringed United States Patent No. 4,792,525, Claim 8; United States Patent No. 4,879,237, Claims 4 and 8; United States Patent No. 5,695,997, Claims 15, 16, 17, and 18; and United States Patent No. 4,789,734, Claim 1.

2. Defendant Merck KGaA infringed United States Patent No. 4,792,525 by importing into the United States after January 1, 1996, peptides which infringe Claim 8 of United States Patent No. 4,792,525.

3. Defendant Merck KGaA has induced infringement of United States Patent No. 4,792,525, Claim 8; United States Patent No. 4,879,237, Claims 4 and 8; United

States Patent No. 5,696,997, Claims 15, 16, 17, and 18; and United States Patent No. 4,789,734, Claim 1.

4. Claim 8 of United States Patent No. 4,792,525 has not been proven invalid. Claim 1 of United States Patent No. 4,789,734 has not been proven invalid. Claims 4 and 8 of United States Patent No. 4,879,237 have not been proven invalid. Claims 15, 16, 17, and 18 of United States Patent No. 5,696,997 have not been proven invalid.

5. Defendant Dr. David A. Cheresh and defendant The Scripps Research Institute are dismissed.

6. Plaintiffs are entitled to recover from Merck KGaA $15,000,000 in damages to compensate plaintiffs for Merck's infringement and inducing infringement.

7. Plaintiffs are entitled to recover against Merck KGaA prejudgment interest through April 30, 2000, in the amount of $1,125,000, with further prejudgment interest accruing from April 30, 2000 computed by the formula $(16{,}125{,}000 \times 1.00008777^{y}) - 16{,}125{,}000$ where y is the number of days from April 30, 2000 to the entry of judgment, and postjudgment interest from the date of this judgment until paid.

Date: March 26, 2001

s/ James M. Fitzgerald
Senior United States District Judge

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

02-1052, -1065

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE,

Plaintiffs-Cross Appellants,

and

TELIOS PHARMACEUTICALS, INC.,

Plaintiff-Appellee,

v.

MERCK KGaA,

Defendant-Appellant,

and

THE SCRIPPS RESEARCH INSTITUTE and DR. DAVID A. CHERESH,

Defendants.

ORDER

A combined petition for panel rehearing and for rehearing en banc having been filed by the APPELLANT, and a response thereto having been invited by the court and filed by the CROSS-APPELLANTS* and the petition for rehearing having been referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc and

response having been referred to the circuit judges who are in regular active service,

UPON CONSIDERATION THEREOF, it is

ORDERED that the petition for panel rehearing be, and the same hereby is, DENIED and it is further

ORDERED that the petition for rehearing en banc be, and the same hereby is, DENIED.

The mandate of the court will issue on December 10, 2003.

Circuit Judge SCHALL did not participate in the vote.

FOR THE COURT,

s/Jan Horbaly
Jan Horbaly, Clerk

Dated: December 3, 2003

cc: Donald R. Dunner
Mauricio A. Flores
Kelly Morron, Stanto Lawrence, III
William R. Boudreaux

INTEGRA LIFESCIENCES V MERCK, 02-1052, -1065 (DCT -96-CV-1307)

*Amicus curiae briefs were filed by Eli Lilly and Company, Wyeth, and The Association of the Bar of the City of New York.

Note: Pursuant to Fed. Cir. R. 47.6, this order is not citable as precedent. It is a public record.

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

02-1052, -1065

INTEGRA LIFESCIENCES I, LTD. and THE BURNHAM INSTITUTE,

Plaintiffs-Cross Appellants,

and

TELIOS PHARMACEUTICALS, INC.,

Plaintiff-Appellee,

v.

MERCK KGaA,

Defendant-Appellant,

and

THE SCRIPPS RESEARCH INSTITUTE and DR. DAVID A. CHERESH,

Defendants.

JUDGMENT

ON APPEAL from the United States District Court for the Southern District of California

In CASE NO(S) 96-CV-1307

This CAUSE having been heard and considered, it is

ORDER and ADJUDGED:

AFFIRMED-IN PART, REVERSED-IN-PART, and REMANDED

ENTERED BY ORDER OF
THE COURT

December 3, 2003
Date

s/Jan Horbaly
Jan Horbaly, Clerk

ISSUED AS A MANDATE: December 10, 2003